The Perspective of Pathophysiology - Guided Stroke Therapy

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Introduction: Why is clinical stroke therapy failing so often?

Treatment of patients with acute stroke is still far from being satisfactory. This is surprising since from experimental studies in animals a plenitude of substances is known to be therapeutically efficient in acute stroke. One of the most important reasons for this discrepancy is probably the extreme pathophysiological heterogeneity of human stroke. It is well known that drugs which are therapeutically efficient in one particular "pathophysiological situation" can be less beneficial or even harmful in other situations. Thus, the attempted "one drug for one disease" approach used in clinical trials may be inadequate for the acute stroke condition. The logical consequence of this is the attempt to identify pathophysiological processes in patients with acute stroke on an individual basis and to treat patients accordingly with the drug effective in the specific pathophysioglocial condition: *The perspective of pathophysiology – guided stroke therapy.*

Pathophysiology in acute stroke

The primary pathophysiological distinction is between hemorrhagic and ischemic stroke. In this lecture the main focus is on the more frequent **ischemic stroke**: A schematic (and simplified) overview on pathophysiological processes in this condition is given in Figure 1 which is modified after Dirnagl et al. 1999.

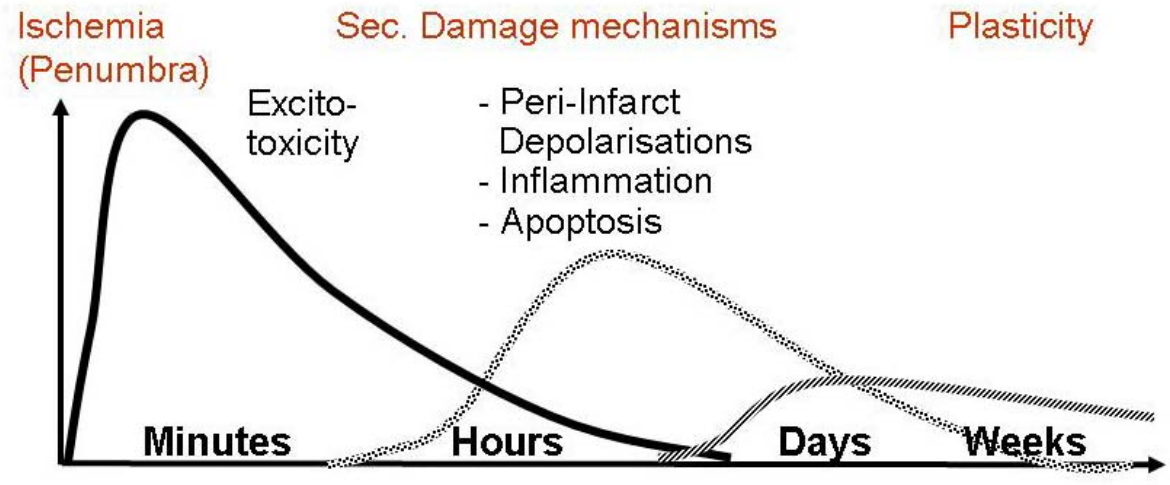

*Fig. **1:** Pathophysiologal events in acute ischemic stroke (modified after Dirnagl et al. 1999)*

The primary pathophysiological event (from the perspective of the affected tissue) is the onset of cerebral **ischemia** which rapidly leads to loss of energy supply and a lack removal

of (potentially toxic) waste. In the first minutes to hours after stroke onset, the pathophysiological picture is frequently dominated by direct consequences of this initial event. However, ischemia triggers further processes which in themselves can lead to further damage, i.e. **secondary damage mechanisms**, most notably, excitotoxicity, peri-infarct depolarizations (PID), inflammation, and apoptosis. In experimental studies, it has been clearly shown that suppression of these events (in the appropriate time window) is associated with significantly less final damage to the tissue. After damage has occurred, the brain uses repair and compensation mechanisms to eventually achieve recovery of function despite of tissue damage (**plasticity**).

Pursuing the idea of pathophysiology-guided stroke therapy thus means to identify above mentioned pathophysiological events and to tailor treatment accordingly. This approach is being illustrated subsequently for each of the three major pathophysiological phases after stroke:

Immediate consequences of cerebral ischemia: Penumbra, mismatch, inverse mismatch

Cerebral ischemia which accompanies ischemic stroke is remarkably different from the one which occurs after a cardiac arrest (focal versus global cerebral ischemia). During global ischemia, cerebral perfusion is almost immediately reduced to zero in the entire brain. In focal ischemia, however, the situation is characterized by areas in which ischemia is almost complete and leads to cell death within few minutes (**infarct core**), but also areas in which – due to collateral circulation – perfusion is partly restored, albeit at reduced levels. These latter areas can be further subdivided into those in which the reduction in perfusion does not lead to any metabolic or functional disturbances, and those in which the perfusion disturbance has led to metabolic and functional deficits, the latter being termed, the **ischemic penumbra**. The ischemic penumbra is thus an area which can still be saved, however, which is at risk of permanent damage. Typically, if no (spontaneous or drug-induced) reperfusion occurs, in subsequent hours, the infarct core will grow into the area of the penumbra (see Fig. 2).

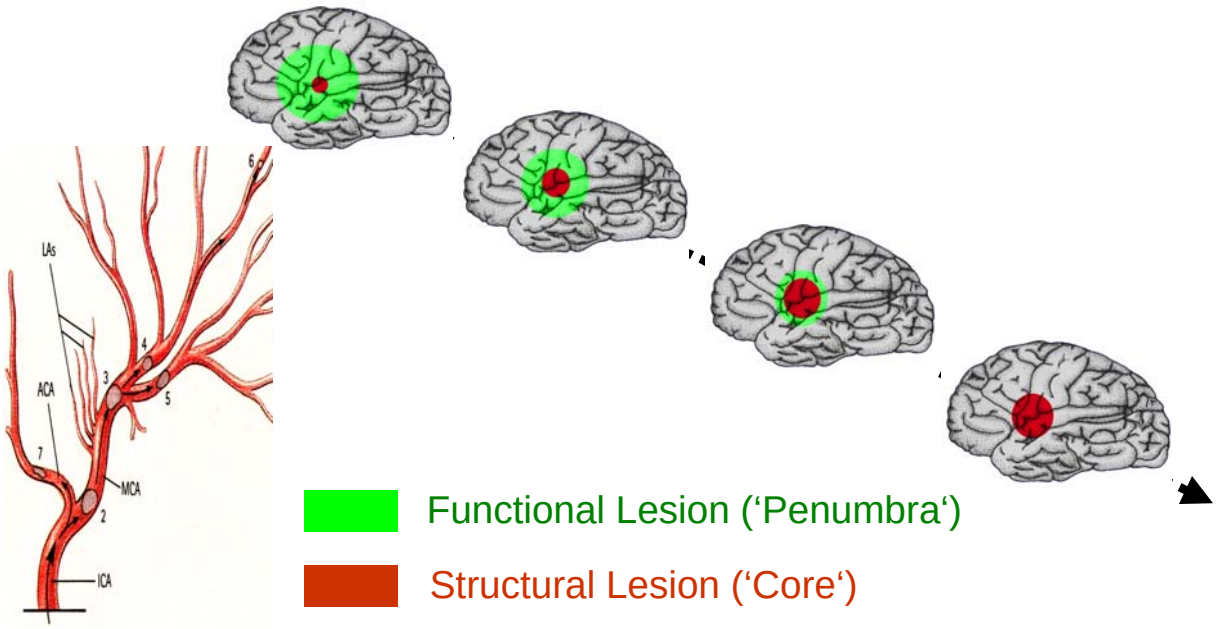

Fig. 2: Infarct Core and Penumbra in Acute Ischemic Stroke

The only (FDA-approved) therapy of acute stroke is systemic fibrinolysis, which, however, is only to be given within the first three hours after stroke onset. The pathophysiological rationale behind this time window is the high likelyhood at this time interval that there is still a viable penumbra. While statistically, this is correct, there is profound intersubject variability and this variability becomes even more relevant at later time points, when there is still a good portion of subjects in whom a large penumbra is present, however, the overall likelihood is smaller. It is particularly in these subjects that one would like to identify the presence/absence of the penumbra in the individual patient and perform fibrinolysis subsequently only in those with a large penumbra.

Developments in MRI have made it possible to define a brain area which seems a reasonable estimate of the penumbra. Diffusion-weighted MRI in acute stroke turned out to indicate an area of severe metabolic disturbance, probably already affected by cytotoxic edema, and thus this parameter seems a good operational definition of the infarct core. Perfusion-weighted MRI, especially based on Dynamic Susceptibility Contrast (DSC)-MRI, on the other hand, gives a good estimate of the brain regions affected by the perfusion disturbance. Perfusion-lesion minus the Diffusion-lesion is thus a reasonable first operational estimate of the penumbra. In order to emphasize the operational character, it is termed ***mismatch*** area. Based on this operational definition results of several clinical studies now suggest that the temporal window of systemic fibrinolysis in those patients with a large mismatch area may be extended to 6 or perhaps 9 hours. In these patients, the perfusion disturbance seems to be the dominating pathophysiological process and therefore rapid reperfusion is the most important therapeutic measure.

A different pathophysiological situation may dominate in small infarcts. In a consecutive series of 18 patients with small ischemic stroke in sub cortical areas, the diffusion lesion was consistently larger than the perfusion lesion (**inverse mismatch**). Figure 3 illustrates a potential explanation for this finding. An initially small perfusion lesion in an end artery leads to necrosis and release of cytotoxic substances. This induces cellular damage in areas beyond the initial ischemic lesion. If this explanation is correct, then these patients would be ideal candidates for neuroprotective therapy, since secondary damage mechanisms as schematically given in Fig 1 above are probably the dominant pathophysiological factor.

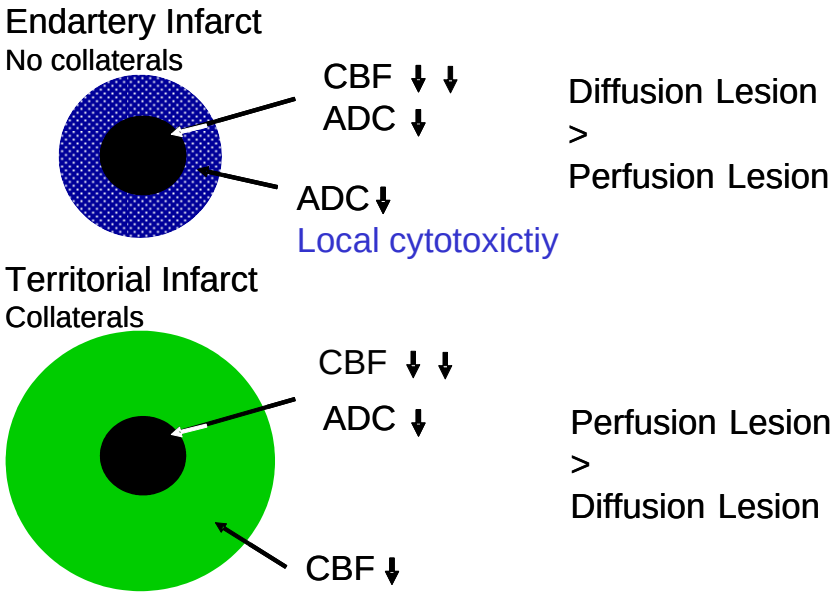

Figure 3. Inverse Mismatch versus Mismatch: Hypothesis for underlying pathophysiolgoy

Secondary Damage Mechanisms

The initial ischemic event triggers secondary damage mechanisms which lead to cell damage independently of the lack of oxygen and/or nutrients. Among others, the following secondary mechanisms have been described in animal models of stroke:

(1) **Excitotoxicity** is due to the accumulation of excitatory amino acids such as glutamate and aspartate which induce an abnormally high elevation of intracellular calcium concentration leading to subsequent cell damage.

(2) In the surround of the infarct core, accumulation of potassium can lead to spontaneous depolarizations of brain tissue similar to the well-known phenomenon of spreading depression (SD). When SDs occur in “normal” brain tissue, the increased energy demand is met by a profound increase in cerebral blood flow, in **Peri-Infarct-Depolarizations (PID)** which typically occur in an area of reduced CBF (in the penumbra zone), it is not possible to meet the increased energy demands by an appropriate blood flow increase. Therefore, the occurrence of PIDs is associated with an increase of the size of the infarct core at the expense of the penumbra. So far, this phenomenon has been described unambiguously in experimental stroke models, only, and is awaiting confirmation in humans. However, in other pathological conditions, notably head trauma and subarachnoid hemorrhage, is has now been shown to occur in humans also, and to be associated with damage.

(3) Another secondary damage mechanism, local **inflammation**, is well established to occur, both in animal models, but also in humans.

(4) **Apoptosis** means, that the initial ischemic event induces expression of genes which eventually lead to cell death. Apoptosis can be clearly differentiated from necrosis since in the former cells due not swell, but rather “break down”. Again it should be noted that the induction of apoptosis can occur in cells which have survived ischemia (e.g. due to reperfusion), and thus may be responsible for secondary clinical deterioration.

For each of the above mentioned processes it has been shown in animal experiments that its respective blockade can be associated with a marked beneficial effect on stroke size and clinical outcome. However, all clinical studies in which such neuroprotective agents were used have failed so far. The most crucial issues seems the selection of the “right” patient according to the ongoing pathophysiological process. Therefore, efforts are being undertaken to identify those pathophysiological processes noninvasively in human patients.

Towards identification of secondary damage mechanisms in humans

Significant progress has been made to identify peri-infarct depolarizations. In animal studies, several non invasive methods have been employed to detect/monitor PIDs. Thus, the effect of PIDs on cerebral tissue can be seen in diffusion-weighted MRI, the influence of PIDs on haemoglobin oxygenation can be detected with near-infrared optical spectroscopy as well as with BOLD- and/or perfusion-weighted MRI. The depolorisation process itself is best identified with electrophysiological methods such as DC-EEG or DC-MEG. Several of these methods are now used in humans to search for PIDs. In the meantime, by means of invasive electrophysiology, it has recently been shown for the first time, that PIDs actually occur in humans, at least after brain trauma and subarachnoid hemorrhage. These recent findings are motivation for further application of the non invasive (bedside) approaches to achieve monitoring of PIDs.

In-vivo identification of the other secondary damage mechanisms, touches on the rapidly evolving field of molecular and cellular brain imaging. Tracers have been developped to detect microglial infiltration with PET as an indicator of local **inflammation**. By employing iron-oxide based contrast agents, labelling of inflammatory cells has also been performed in animal as well as human MRI studies.

Several studies are trying to employ the **apoptosis** marker annexin V. It is labelled either radioactively or with iron-oxide particles to be detected in PET or MRI, respectively. Another approach for molecular brain imaging is near-infrared based fluorescence imaging for which the respective marker has to be labelled with a fluorescent dye. It has recently been shown that detection of fluorescence is possible even noninvasively in the adult. While limited to the brain cortex just below the skull, it will offer an approach for bedside molecular imaging.

In conclusion, while still in an early phase of development, a plenitude of rapidly developping methods will allow us to visualize the presence/absence of secondary damage mechanisms in human stroke.

Plasticity

The clinical outcome after stroke not only depends on the location and extent of the ischemic damage, but also on the efficiency of endogenous mechanisms for compensation and functional recovery. It is well known that after an ischemic stroke, structural and functional changes not only occur in the area of the infarction but also in widespread regions throughout the brain. By using, structural and functional neuroimaging methods, slowly, we are starting to understand these processes of neuronal plasticity. More and more studies are starting to suggest that specific findings in fMRI may be of prognostic value, but they may also be of used for monitoring and guiding physiotherapy.

Functional imaging studies such as fMRI, PET – while being already of great value – do not measure the actual neurophysiological processes in the brain, but rather assess the vascular response. The fact that the relationship between neuronal activity and the vascular response (the neurovascular coupling) may be altered in stroke and stroke prone patients adds to the uncertainty regarding the neurophysiological basis of these vascular signals. It is thus important to add neurophysiological meaning to these signals. One general approach to do this, is to take advantage of integration with electrophysiological methods such as in simultaneous EEG-fMRI. This allows for example to identify the strength of background acitivity (e.g. alpha rhythm Mu rhythm), evoked field potentials, and – in some instances – for the identification of spike bursts simultaneously with fMRI.

I believe that this approach – i.e. adding neurophysiogological information to fMRI/PET signals - will significantly improve our ability to use functional brain imaging for the rapidly developping clinical field of imaging-guided rehabilitation.

Further Reading

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